Gastroenterology 2016;150:1135–1146

Effects of Cancer Stage and Treatment Differences on Racial Disparities in Survival From Colon Cancer: A United States Population-Based Study

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BACKGROUND & AIMS: We evaluated differences in treatment of black vs white patients with colon cancer and assessed their effects on survival, based on cancer stage. **METHODS:** We collected data from the Surveillance, Epidemiology, and End Results–Medicare database and identified 6190 black and 61,951 white patients with colon cancer diagnosed from 1998 through 2009 and followed up through 2011. Three sets of 6190 white patients were matched sequentially, using a minimum distance strategy, to the same set of 6190 black patients based on demographic (age; sex; diagnosis year; and Surveillance, Epidemiology, and End Results registry), tumor presentation (demographic plus comorbidities, tumor stage, grade, and size), and treatment (presentation plus therapies) variables. We conducted sensitivity analyses to explore the effects of socioeconomic status in a subcohort that included 2000 randomly selected black patients. Racial differences in treatment were assessed using a logistic regression model; their effects on racial survival disparity were evaluated using the Kaplan–Meier method and the Cox proportional hazards model. **RESULTS:** After patients were matched for demographic variables, the absolute 5-year difference in survival between black and white patients was 8.3% (white, 59.2% 5-y survival; blacks, 50.9% 5-y survival) ($P < .0001$); this value decreased significantly, to 5.0% ($P < .0001$), after patients were matched for tumor presentation, and decreased to 4.9% ($P < .0001$) when patients were matched for treatment. Differences in treatment therefore accounted for 0.1% of the 8.3% difference in survival between black and white patients. After patients were matched for tumor presentation, racial disparities were observed in almost all types of treatment; the disparities were most prominent for patients with advanced-stage cancer (stages III or IV, up to an 11.1% difference) vs early stage cancer (stages I or II, up to a 4.3% difference). After patients were matched for treatment, there was a greater reduction in disparity for black vs white patients with advanced-stage compared with early-stage cancer. In sensitivity analyses, the 5-year racial survival disparity was 7.7% after demographic match, which was less than the 8.3% observed in the complete cohort. This reduction likely was owing to the differences between the subcohort and the complete cohort in those variables that were not included in the demographic match. This value was reduced to 6.5% ($P = .0001$) after socioeconomic status was included in the demographic match. The difference decreased significantly to 2.8% ($P = .090$) after tumor presentation match, but was not reduced further after treatment match. **CONCLUSIONS:** We observed significant disparities in treatment and survival of black vs white patients with colon cancer. The disparity in survival appears to have been affected more strongly by tumor presentation at diagnosis than treatment. The effects of treatment differences on disparities in survival were greater for patients with advanced-stage vs early-stage cancer.

Keywords: Race; Colorectal Cancer; CRC; Outcome.

As the second leading cause of cancer death in the United States, colorectal cancer (CRC), including colon and rectal cancers, disproportionally has affected black men and women for more than 20 years.[1–3] Black patients have a higher CRC incidence, often are diagnosed at more advanced stages, and have worse overall outcomes than white patients.[3–5] Although some biological differences have been proposed to exist between black and white CRC patients,[6] it has been shown that socioeconomic and sociodemographic status may be the major driving factors for disparities in both CRC incidence and outcomes.[7–10] For instance, sociodemographic status can affect many risk and protective factors for CRC such as lifestyle factors (diet and exercise) and health care utilization (screening, diagnosis, and treatment).[11,12] It is important to identify those factors relating to socioeconomic and sociodemographic status that

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Abbreviations used in this paper: CRC, colorectal cancer; PR, prevalence ratio; SEER, the Surveillance, Epidemiology, and End Results; SES, socioeconomic status.

Most current article

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0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.01.030

can be modified, to facilitate the design and implementation of appropriate policies and interventions to minimize racial disparities in CRC patients.

Treatment is an important modifiable factor that may be affected by socioeconomic and sociodemographic status.[11–13] There have been many inconsistencies reported regarding treatment disparities and their impact on outcome disparities in CRC patients. The treatment disparities between black and white CRC patients have been reported mainly in population-based studies.[14,15] However, studies conducted in single institutions usually reported no apparent treatment disparities between black and white CRC patients.[16–18] Moreover, how equal treatment affects disease outcomes also is reported inconsistently. For example, a recent study showed that the survival disparity between black and white metastatic CRC patients might be explained fully by physician consultation and treatment differences.[4] Mack et al[19] reported that in stage III colon cancer patients who received oxaliplatin, black patients appeared to have even better survival than white patients, indicating that differential receipt and effectiveness of oxaliplatin-containing regimens may not contribute to the poorer survival observed in black than white colon cancer patients. In contrast, several other studies found that black patients had lower survival rates even when similar treatments were provided.[6,16,20] The controversial findings from these studies may be explained partially by differences in the types of treatments analyzed, number of confounding variables considered, and relatively small number of black patients included in model-based studies. For example, Silber et al[21] suggested that a model based on a population dominated by white patients "would be a model that mostly describes what happens to whites."[22] In this study, to address these controversies, we used the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER)–Medicare linked database to evaluate the treatment disparities between black and white colon cancer patients, as well as their impact on racial survival disparity. Taking advantage of an innovative minimum distance matching strategy, we drew from a pool of 61,951 white patients to match 3 distinct white comparison cohorts to a cohort of 6190 black patients. By achieving very close matches between black and white colon cancer patients, we bypassed the need for the model-based analyses used in most previous studies.

Materials and Methods

Study Population and 3 Sets of Matching Variables: Demographics, Tumor Presentation, and Treatment

The details of the study population are described in the Supplementary Material. Briefly, the study cohort included patients aged 66 years or older with histologically confirmed colon cancer diagnosed between 1998 and 2009 identified from the National Cancer Institute SEER–Medicare database. The detailed patient selection procedure is summarized in Figure 1. Details on the 3 sets of matching variables are described in the Supplementary Material. The corresponding codes to identify treatment procedures and drugs used in this study are listed in Supplementary Table 1.

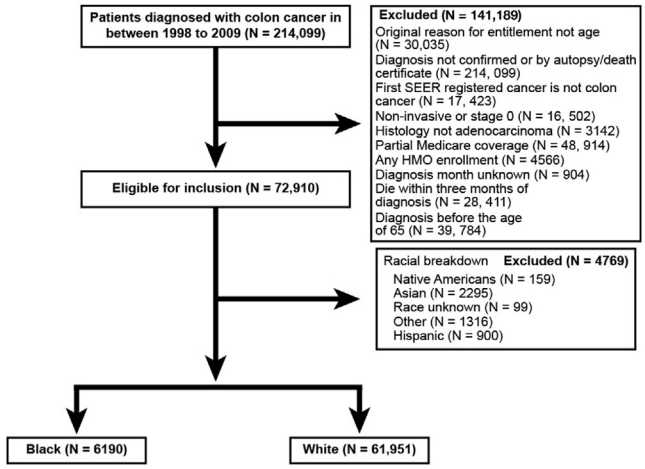

Figure 1. Cohort definition and exclusions.

Survival Outcomes

The primary outcomes were overall 2-, 3-, and 5-year survival. We set our study starting time to be 90 days after cancer diagnosis. Patients who died within 90 days were excluded because of the possible insufficient time for them to receive cancer-related treatment. Survival time was defined as the number of months from the study starting time until the date of death from any cause, or until the end of the observation period. To ensure the completeness and accuracy of death information, we defined our study's observation window until SEER's last follow-up date, December 31, 2011, which ensured at least a 2-year follow-up period for each patient. Patients alive at the end of the follow-up period were censored.

Statistical Analysis

A sequential matching process was conducted similar to the methodology described by Silber et al.[21] We included all 6190 black patients for each match, so the blacks were constant and fully representative of black patients in the SEER population. In comparison, the white comparison cohort changed according to the variables used in each match, and 61,951 white patients made it possible to achieve adequate matches to the 6190 black patients. We matched 3 sets of comparison cohorts by minimizing the overall distance between black and white patients based on demographic-, presentation-, and treatment-related variables. The variables in the demographic match included age, sex, year of diagnosis, and SEER registries. The variables in the presentation match included all the variables in the demographic match, plus individual comorbidities, overall comorbidity score, and tumor characteristics (tumor stage, grade, and size). The variables in the treatment match included all the variables in the presentation match, plus surgery, radiation therapy, targeted therapy, and individual types of common cytotoxic chemotherapy. This novel matching approach finds an optimal match that minimizes the total covariate distance within matched pairs,[23] which is performed by defining a special patterned distance

matrix and passing it to a subroutine to implement the optimal assignment algorithm. The optimal assignment algorithm is implemented using the PROC OPTNET function in SAS (SAS Institute, Cary, NC), which works by minimizing the overall distance between the blacks and whites[21] to ensure the matching of the optimal pairs of white and black patients. Propensity scores derived from the logistic regression of blacks vs whites on the variables to be controlled in the matching were used to calibrate the distance before assigning whites to blacks according to minimum distance. The quality of the matching was verified carefully (Supplementary Tables 2 and 3). Racial differences in treatment were assessed using the logistic regression model. Prevalence ratios (PRs) and corresponding 95% confidence intervals were estimated. The overall survival curve was plotted using the Kaplan–Meier method.[24] Survival difference was tested with the log-rank test.[25,26] The association between ethnicity and 5-year survival for colon cancer patients in each matching was evaluated using hazard ratios and 95% confidence intervals calculated by the Cox proportional hazards model. Sensitivity analyses were conducted to explore the impacts of socioeconomic status (SES) in a subcohort including 2000 randomly sampled black patients. SAS (version 9.4) and STATA (version 11.0; STATA Corp, College Station, TX) software packages were used for the analyses in this study. All P values were 2-sided. A P value of less than .05 was considered to indicate a statistically significant difference.

Results

Overall Matching Results

This study included a total of 68,141 patients who were newly diagnosed with colon cancer from 1998 to 2009 and met the inclusion criteria (Figure 1). Among them, 6190 (9.1%) were black and 61,951 (90.9%) were white (excluding Caucasian with Spanish origin/surname). Three sets of 6190 white comparison cohorts were identified and matched sequentially to the same set of 6190 black patients according to the approach as previously described.[21] Supplementary Table 2 summarizes patient characteristics from the entire population of black patients and each of the 3 sets of white comparison cohorts selected from the entire population of white patients. Patient characteristics stratified by tumor stage are summarized in Supplementary Table 3. As suggested by Silber et al,[21] a 10% standardized difference (defined as the mean difference between black and white patients as a fraction of the SD before matching) was used as a cut-off value to assess the balance of covariates after matching. The controlled variables in each match in this study were closely balanced, with less than 0.1 standardized differences to ensure that all matches were successful (Supplementary Tables 2 and 3). The aspects of disparity between black and white patients were removed sequentially in the 3 white matches. The characteristics that were not controlled in each match, and those characteristics unobservable in our data set, reflected the possible sources of disparity between blacks and whites (see the Supplementary Material for examples of how to interpret sequential matching results).

Treatment Disparity in the Overall Population and Stratified by Cancer Stage

Compared with presentation-matched white patients, black patients had a lower rate of receiving most treatments, including surgery (88.5% vs 91.4%; $P < .0001$), targeted therapy (3.3% vs 4.4%; $P = .002$), and most of the individual types of cytotoxic chemotherapies (Supplementary Table 2). There were very few patients (0.3%) who received capecitabine for both black and presentation-matched white patients, and it was the only chemotherapy agent that was not differentially received by black and white patients (Supplementary Table 2). Moreover, there was a significantly higher percentage of black patients who did not have evidence of receiving any antitumor treatment for their colon cancer (8.5%) than demographic-matched whites (4.8%) and presentation-matched whites (5.5%) ($P < .0001$) (Supplementary Table 2). Table 1 lists the detailed treatment disparities by cancer stage between black and presentation-matched whites. The matching quality was adequate, as shown in Supplementary Table 3. After controlling for tumor characteristics and comorbidities, advanced-stage (III/IV) patients showed a more pronounced pattern of treatment disparity compared with early-stage (I/II) patients (Table 1). Stage I black patients had a lower surgery rate than presentation-matched white patients (92.5% vs 95.7%; $P = .0003$). There was no statistical difference in surgery in stages II, III, and IV patients. Stage II black patients received less chemotherapy than matched white patients (18.1% vs 22.4%; $P = .001$); although the magnitude of the difference was small (4.3%). Stage III black and white patients showed a significant difference in the use of chemotherapy (53.1% vs 64.2%; $P < .0001$), with a large absolute difference (11.1%), including fluorouracil/capecitabine alone (32.9% vs 41.2%; $P < .0001$) and fluorouracil/capecitabine plus oxaliplatin (15.2% vs 19.0%; $P = .005$). Remarkable differences also were observed in stage IV patients using chemotherapy (56.1% vs 63.3%; $P = .001$) including fluorouracil/capecitabine plus oxaliplatin (17.9% vs 24.7%; $P = .0002$) and irinotecan (12.1% vs 18.5%; $P < .0001$), as well as targeted therapy agents (15.6% vs 21.1%; $P = .002$) (Table 1).

Survival Disparity Between Black and Sequentially Matched White Patients in the Overall Population

Figure 2 shows the survival curves of all black patients and 3 sets of sequentially matched white patients. Table 2 summarizes patient survival; median survival time; 2-, 3-, and 5-year survival rates; the absolute survival rate differences between each matched set of white and black patients; and hazard ratios calculated with the Cox proportional model. As shown in Figure 2, there was a significant survival difference between black and demographic-matched white patients (absolute 5-year survival rate difference, 8.3%; $P < .0001$) (Table 2). This difference was reduced dramatically after presentation match (5.0%; $P < .0001$) (Table 2), but was only slightly reduced

Table 1. Treatment and SES Disparities Between Black and Presentation-Matched White Colon Cancer Patients by Cancer Stage

Variable	Black patients (%)	Matched white patients (%)	PR (95% CI)	*P* value
Stage I (N = 1462, each)				
Surgery	1353 (92.5)	1399 (95.7)	1.03 (1.02–1.05)	**.0003**
SES				
High	292 (20.0)	835 (57.1)	2.86 (2.56–3.20)	**<.0001**
Stage II (N = 1818, each)				
Surgery	1791 (98.5)	1799 (99.0)	1.00 (1.00–1.01)	.24
Chemotherapy	329 (18.1)	408 (22.4)	1.24 (1.09–1.41)	**.001**
SES				
High	344 (18.9)	986 (54.2)	2.87 (2.58–3.18)	**<.0001**
Stage III (N = 1546, each)				
Surgery	1536 (99.4)	1541 (99.7)	1.00 (1.00–1.01)	.20
Chemotherapy	821 (53.1)	993 (64.2)	1.21 (1.14–1.28)	**<.0001**
Fluorouracil/capecitabine alone	508 (32.9)	637 (41.2)	1.25 (1.14–1.38)	**<.0001**
Fluorouracil/capecitabine plus oxaliplatin	235 (15.2)	294 (19.0)	1.25 (1.07–1.46)	**.005**
Irinotecan[a]	38 (2.5)	53 (3.4)	1.39 (0.93–2.10)	.11
Targeted therapy	33 (2.1)	39 (2.5)	1.18 (0.75–1.87)	.47
SES				
High	277 (17.9)	842 (54.5)	3.04 (2.71–3.41)	**<.0001**
Stage IV (N = 983, each)				
Surgery	703 (71.5)	731 (74.4)	1.04 (0.99–1.10)	.16
Chemotherapy	551 (56.1)	622 (63.3)	1.13 (1.05–1.21)	**.001**
Fluorouracil/capecitabine alone	290 (29.5)	322 (32.8)	1.11 (0.97–1.27)	.12
Fluorouracil/capecitabine plus oxaliplatin	176 (17.9)	243 (24.7)	1.38 (1.16–1.64)	**.0002**
Irinotecan[a]	119 (12.1)	182 (18.5)	1.53 (1.24–1.89)	**<.0001**
Targeted therapy	153 (15.6)	207 (21.1)	1.35 (1.12–1.64)	**.002**
SES				
High	204 (20.8)	537 (54.6)	2.63 (2.30–3.01)	**<.0001**

NOTE. The 381 black patients with unknown stage are not included in stage-stratified analyses. Significant effects ($P < .05$) are shown in bold.
CI, confidence interval.
[a]The patients using irinotecan alone could not be distinguished from patients using irinotecan with targeted therapy.

after further matching on treatment (4.9%; $P < .0001$) (Table 2). Therefore, after demographic match, the percentage of the 5-year survival disparity explained by treatment was much smaller (1.2%) than that explained by presentation (39.8%) (Table 2). Consistently, the 5-year survival curve for treatment-matched whites almost overlapped with that of presentation-matched whites (Figure 2). Very similar patterns of survival disparity changes over sequential matching also were noted in the 2- and 3-year survival analyses (Table 2).

Survival Disparity Between Black and Sequentially Matched White Patients by Cancer Stage

Supplementary Figure 1 shows the survival curves by cancer stage for black patients and the 3 sets of sequentially matched white patients. Table 3 lists the 2-, 3-, and 5-year survival rates for black and matched white patients in each stage as well as their survival differences. The detailed matching properties are listed in Supplementary Table 3. Survival disparity between black and demographic-matched white patients was apparent for all 4 stages (Supplementary Figure 1). The differences in survival were statistically significant in almost all analyses except for 3- and 5-year survival rates in stage IV patients with borderline significances ($P = .13$ and .095, respectively), likely owing to the heterogeneity (eg, disease and treatment history), as well as the much smaller number of stage IV patients with a long survival. For stage I patients, presentation-match substantially reduced the racial survival difference (4.5% to 2.5%, 5.8% to 3.0%, and 7.3% to 4.7%, for 2-, 3-, and 5-year survival rates, respectively), which was reduced only modestly on further treatment match (2.5% to 1.1%, 3.0% to 2.0%, and 4.7% to 4.2%, respectively) (Table 3 and Supplementary Figure 1*A*). For stage II patients, the sequential match on presentation and then treatment resulted in sequential but modest reductions in racial survival disparity (4.7% to 2.7% to 2.8%, 5.8% to 4.1% to 3.6%, and 6.6% to 4.6% to 4.0%, for 2-, 3-, and 5-year survival rates, respectively) (Table 3 and Supplementary Figure 1*B*), with patterns close to those observed in stage I patients. In sharp contrast, for stage III patients, presentation match did not substantially narrow the survival disparity but further treatment match did (4.0% to 4.5% to 2.2%, 3.9% to 3.1% to 2.0%, and 5.1% to 4.3% to 2.8%, for 2-, 3-, and 5-year survival rates, respectively) (Table 3 and Supplementary Figure 1*C*), suggesting that the observed

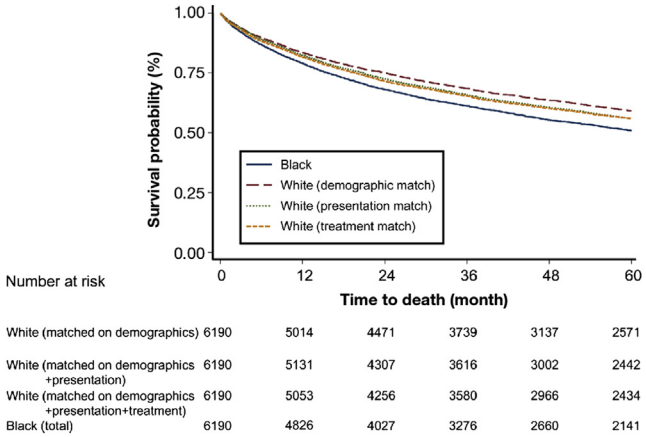

Figure 2. Kaplan–Meier plot for the 5-year survival rates of all black colon cancer patients and the 3 sets of matched white patients diagnosed between 1998 and 2009. *Blue solid line*, all black patients; *red long dashed line*: demographic-matched white patients; *green dotted line*, presentation-matched white patients; *orange dashed line*, treatment-matched white patients.

treatment disparity (Table 1) had a dramatic effect on the survival disparity in stage III patients. A similar effect by treatment match on survival disparity was observed for stage IV patients (3.5% to 0.4%, 2.6% to 0.2%, and 0.5% to -0.2%, for 2-, 3-, and 5-year survival rates, respectively) (Table 3 and Supplementary Figure 1*D*). Consistently, after demographic match, the percentage of the 3-year survival disparity explained by presentation and treatment was 48.3% and 17.2%, respectively, for stage I patients, and 29.3% and 8.6% for stage II patients, whereas it was 20.5% and 28.2% for stage III patients, and 10.3% and 82.8% for stage IV patients (Table 3). These data further indicated that, compared with the survival disparity explained by tumor presentation, the survival disparity explained by treatment difference was much smaller in early-stage but larger in advanced-stage patients. Similar patterns of the stage-specific effect by presentation and treatment also were apparent in most 2- and 5-year analyses, with the only exception being in the 5-year analysis for stage IV patients, most likely owing to the small percentage of stage IV patients surviving for 5 years.

The Confounding Effects of SES, Marital Status, and Urban/Rural Residence

SES, marital status, and urban/rural residence are major factors that have been associated significantly with colon cancer racial disparity[8,11,27,28] and thus are major confounders in our analyses. Because these variables are, as expected, highly different between blacks and whites (Table 1 and Supplementary Tables 2 and 3),[8,27] adding them to the matching made it impossible to achieve balanced matches if we used the full set of 6190 black patients. To evaluate their effects on our analyses, we conducted a subcohort analysis in which we randomly sampled 2000 black patients from the full set of 6190 black patients, and then used the entire white population (N = 61,951) to match to the sampled black patients. By reducing the number of black patients, we increased the ratio of the number of white to black patients so that we were able to achieve adequate matches on all variables. The randomly sampled 2000 black patients were representative of the full set of 6190 black patients in terms of host characteristics (Supplementary Table 4) and survivals (Supplementary Table 5 and Supplementary Figure 2). It should be noted

Table 2. Two-, Three-, and Five-Year Survival for Black and Matched White Colon Cancer Patients

Outcome measure	Black patients (N = 6190)	Matched white patients: Treatment match (N = 6190)	Presentation match (N = 6190)	Demographic match (N = 6190)
Survival, median (95% CI), *mo*	61.5 (57.9–66.3)	76.5 (72.6–81.3)	77.2 (72.6–82.6)	92.2 (87.2–100.0)
2-year survival, % (95% CI)	68.1 (67.0–69.3)	71.6 (70.4–72.7)	72.5 (71.4–73.6)	75.0 (73.9–76.1)
Survival difference, n (%)		3.5[a] 0.9 (13.0%)[b]	4.4[a] 2.5 (36.2%)[c]	6.9[a]
P value		**<.0001**	**<.0001**	**<.0001**
3-year survival, % (95% CI)	61.1 (59.9–62.4)	65.3 (64.1–66.5)	65.8 (64.6–67.0)	68.5 (67.4–69.7)
Survival difference, n (%)		4.2[a] 0.5 (6.8%)[b]	4.7[a] 2.7 (36.5%)[c]	7.4[a]
P value		**<.0001**	**<.0001**	**<.0001**
5-year survival, % (95% CI)	50.9 (49.6–52.2)	55.8 (54.5–57.1)	55.9 (54.6–57.2)	59.2 (57.9–60.5)
Survival difference, n (%)		4.9[a] 0.1 (1.2%)[b]	5.0[a] 3.3 (39.8%)[c]	8.3[a]
P value		**<.0001**	**<.0001**	**<.0001**
Cox HR (95% CI)	1 (reference)	0.88 (0.84–0.93)	0.87 (0.83–0.91)	0.79 (0.75–0.83)

NOTE. Significant effects ($P < .05$) are shown in bold.
CI, confidence interval; HR, hazard ratio.
[a]Survival differences between black and matched white patients.
[b]The absolute difference (percentage) of survival disparity after demographic match explained by treatment.
[c]The absolute difference (percentage) of survival disparity after demographic match explained by presentation. For example, the absolute 5-year difference of survival disparity after demographic match explained by presentation is 3.3% (8.3%–5.0%), and the percentage is 39.8% (3.3/8.3 × 100%).

Table 3. Two-, Three-, and Five-Year Survival for Black and Matched White Colon Cancer Patients by Stage

		Matched white patients		
	Black patients	Treatment match	Presentation match	Demographic match
Stage I				
2-year survival, % (95% CI)	84.3 (82.3–86.1)	85.4 (83.4–87.1)	86.8 (84.9–88.4)	88.8 (87.1–90.3)
Survival difference, n (%)		1.1[a] 1.4 (31.1%)[b]	2.5[a] 2.0 (44.4%)[c]	4.5[a]
P value		.43	.062	**.0004**
3-year survival, % (95% CI)	79.0 (76.8–81.0)	81.0 (78.9–83.0)	82.0 (79.9–83.9)	84.8 (82.9–86.6)
Survival difference, n (%)		2.0[a] 1.0 (17.2%)[b]	3.0[a] 2.8 (48.3%)[c]	5.8[a]
P value		.18	**.046**	**<.0001**
5-year survival, % (95% CI)	69.0 (66.5–71.5)	73.2 (70.8–75.5)	73.7 (71.3–76.0)	76.3 (74.0–78.5)
Survival difference, n (%)		4.2[a] 0.5 (6.8%)[b]	4.7[a] 2.6 (35.6%)[c]	7.3[a]
P value		**.017**	**.007**	**<.0001**
Cox HR (95% CI)	1 (reference)	0.85 (0.74–0.97)	0.82 (0.71–0.94)	0.72 (0.63–0.84)
Stage II				
2-year survival, % (95% CI)	81.2 (79.3–82.9)	84.0 (82.3–85.7)	83.9 (82.2–85.5)	85.9 (84.2–87.4)
Survival difference, n (%)		2.8[a] -0.1 (-2.1%)[b]	2.7[a] 2.0 (42.6%)[c]	4.7[a]
P value		**.022**	**.028**	**.0001**
3-year survival, % (95% CI)	74.5 (72.4–76.5)	78.1 (76.2–80.0)	78.6 (76.7–80.5)	80.3 (78.4–82.1)
Survival difference, n (%)		3.6[a] 0.5 (8.6%)[b]	4.1[a] 1.7 (29.3%)[c]	5.8[a]
P value		**.011**	**.004**	**<.0001**
5-year survival, % (95% CI)	62.7 (60.3–65.1)	66.7 (64.4–68.9)	67.3 (65.0–69.6)	69.3 (67.0–71.5)
Survival difference, n (%)		4.0[a] 0.6 (9.1%)[b]	4.6[a] 2.0 (30.3%)[c]	6.6[a]
P value		**.019**	**.006**	**.0001**
Cox HR (95% CI)	1 (reference)	0.86 (0.76–0.96)	0.84 (0.75–0.94)	0.77 (0.68–0.87)
Stage III				
2-year survival, % (95% CI)	69.0 (66.6–71.3)	71.2 (68.9–73.4)	73.5 (71.2–75.6)	73.0 (70.7–75.1)
Survival difference, n (%)		2.2[a] 2.3 (57.5%)[b]	4.5[a] -0.5 (-12.5%)[c]	4.0[a]
P value		.19	**.006**	**.016**
3-year survival, % (95% CI)	60.7 (58.1–63.1)	62.7 (60.2–65.1)	63.8 (61.3–66.2)	64.6 (62.1-67.0)
Survival difference, n (%)		2.0[a] 1.1 (28.2%)[b]	3.1[a] 0.8 (20.5%)[c]	3.9[a]
P value		.26	.076	**.025**
5-year survival, % (95% CI)	48.9 (46.2–51.5)	51.7 (49.0–54.3)	53.2 (50.5–55.8)	54.0 (51.3–56.6)
Survival difference, n (%)		2.8[a] 1.5 (29.4%)[b]	4.3[a] 0.8 (15.7%)[c]	5.1[a]
P value		.14	**.024**	**.007**
Cox HR (95% CI)	1 (reference)	0.92 (0.83–1.02)	0.87 (0.78–0.97)	0.87 (0.78–0.96)
Stage IV				
2-year survival, % (95% CI)	25.4 (22.7–28.2)	25.8 (23.1–28.7)	28.9 (26.0–31.8)	29.8 (26.9–32.8)
Survival difference, n (%)		0.4[a] 3.1 (70.5%)[b]	3.5[a] 0.9 (20.5%)[c]	4.4[a]
P value		.83	.092	**.033**
3-year survival, % (95% CI)	16.9 (14.5–19.5)	17.1 (14.7–19.7)	19.5 (17.0–22.2)	19.8 (17.2–22.5)
Survival difference, n (%)		0.2[a] 2.4 (82.8%)[b]	2.6[a] 0.3 (10.3%)[c]	2.9[a]
P value		.91	.16	.13
5-year survival, % (95% CI)	9.9 (7.8–12.2)	9.7 (7.6–12.0)	10.4 (8.3–12.8)	12.7 (10.4–15.2)
Survival difference, n (%)		-0.2[a] 0.7 (25.0%)[b]	0.5[a] 2.3 (82.1%)[c]	2.8[a]
P value		.88	.75	.095
Cox HR (95% CI)	1 (reference)	0.99 (0.90–1.09)	0.92 (0.84–1.01)	0.88 (0.79–0.97)

NOTE. Significant effects ($P < .05$) are shown in bold.
CI, confidence interval; HR, hazard ratio.
[a]Survival differences between black and matched white patients.
[b]The absolute difference (percentage) of survival disparity after demographic match explained by treatment.
[c]The absolute difference (percentage) of survival disparity after demographic match explained by presentation.

that after demographic matching, the racial survival disparity of the subcohort was reduced compared with the complete cohort. For example, the 2-, 3-, and 5-year survival differences of the subcohort vs the complete cohort was 6.5% vs 6.9%, 6.2% vs 7.4%, and 7.7% vs 8.3%, respectively. The reduction likely was owing to the combined effects of the differences between the subcohort and the complete cohort in those variables that were not included in the demographic match. After computing an SES score based on neighborhood poverty, income, and education level to reflect the SES status of the patients, we added the SES to all 3 types of matches and the results of the subcohort analyses

Table 4. Two-, Three- and Five-Year Survival for Sampled Black and Matched White Colon Cancer Patients in the Subcohort Analysis

		Matched white patients						
		Matching including SES						Excluding SES
Outcome measure	Black patients (n = 2000)	Treatment match (n = 2000)		Presentation match (n = 2000)		Demographic match (n = 2000)		Demographic match (n = 2000)
Survival, median (95% CI), mo	64.6 (57.0–75.4)	70.6 (64.3–76.4)		70.1 (62.5–76.1)		90.3 (78.4–107.9)		96.9 (86.5–114.9)
2-year survival, % (95% CI)	67.7 (65.6–69.7)	71.4 (69.3–73.3)		71.3 (69.3–73.3)		73.6 (71.6–75.4)		74.2 (72.2–76.1)
Survival difference, n (%)		3.7[a]	-0.1 (-1.5%)[b]	3.6[a]	2.3 (35.4%)[c]	5.9[a]	0.6 (9.2%)[d]	6.5[a]
P value		**.012**		**.014**		**.0001**		**<.0001**
3-year survival, % (95% CI)	61.7 (59.5–63.8)	64.1 (61.9–66.2)		64.6 (62.4–66.7)		66.1 (64.0–68.2)		67.9 (65.8–69.9)
Survival difference, n (%)		2.4[a]	0.5 (8.1%)[b]	2.9[a]	1.5 (24.2%)[c]	4.4[a]	1.8 (29.0%)[d]	6.2[a]
P value		.12		.059		**.004**		**<.0001**
5-year survival, % (95% CI)	50.9 (48.5–53.2)	54.2 (51.9–56.4)		53.7 (51.4–56.0)		57.4 (55.1–59.7)		58.6 (56.3–60.8)
Survival difference, n (%)		3.3[a]	-0.5 (-6.5%)[b]	2.8[a]	3.7 (48.1%)[c]	6.5[a]	1.2 (15.6%)[d]	7.7[a]
P value		**.049**		.090		**.0001**		**<.0001**
Cox HR (95% CI)	1 (reference)	0.90 (0.82–0.99)		0.91 (0.83–0.99)		0.82 (0.74–0.90)		0.79 (0.72–0.87)

NOTE. Significant effects ($P < .05$) are shown in bold.
CI, confidence interval; HR, hazard ratio.
[a]Survival differences between black and matched white patients.
[b]The absolute difference (percentage) of survival disparity after demographic match explained by SES and treatment.
[c]The absolute difference (percentage) of survival disparity after demographic match explained by SES and presentation.
[d]The absolute difference (percentage) of survival disparity after demographic match explained by SES.

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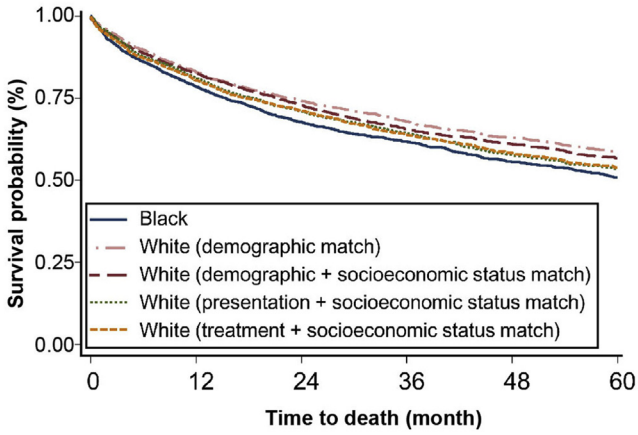

Figure 3. Kaplan–Meier plot for the 5-year survival rates of sampled black colon cancer patients and the 4 sets of matched white patients. *Blue solid line*, 2000 sampled black patients; *pink long dashed and dotted line*, demographic-matched white patients; *red long dashed line*, demographic plus SES-matched white patients; *green dotted line*, presentation plus SES-matched white patients; *orange dashed line*, treatment plus SES-matched white patients.

were highly consistent with those of the main analyses. As shown in Table 4 and Figure 3, when SES was added to the demographic match, the survival difference between blacks and matched whites was reduced from 6.5% to 5.9% (9.2% reduction), from 6.2% to 4.4% (29.0% reduction), and from 7.7% to 6.5% (15.6% reduction), for the 2-, 3-, and 5-year survival rates, respectively. These changes, which were not surprising, support the view that SES plays an important role in colon cancer racial survival disparity. Importantly, tumor presentation match further significantly reduced the survival disparity by 35.4%, 24.2%, and 48.1%, for the 2-, 3-, and 5-year survival rates, respectively, but treatment match did not (Table 4 and Figure 3). These findings are consistent with the results derived from the complete cohort (Table 2 and Figure 2). Similarly, marital status and urban/rural residence also reduced survival disparity in demographic matching, although to a lesser extent than SES (0%, 8.1%, and 6.5% reduction for the 2-, 3-, and 5-year survival rates, respectively) (Supplementary Table 6 vs Table 4 and Supplementary Figure 3 vs Figure 3). Consistently, we also observed that the survival disparity was largely reduced in presentation match (29.2%, 30.6%, and 44.2%, for the 2-, 3-, and 5-year survival rates, respectively), but not treatment match in the subcohort analysis that matched patients on marital status and urban/rural residence (Supplementary Table 6 and Supplementary Figure 3). We further explored the stage-specific effects of these analyses. Because early-stage patients showed similar survival disparity patterns and advanced-stage patients showed similar patterns (Table 3), we combined early-stage patients together and advanced-stage patients together to increase the sample sizes and thus the reliability of these analyses. Supplementary Table 7 showed that, in the subcohort analyses after matching on SES or marital status and urban/rural residence, racial difference in treatment still existed, especially for the use of chemotherapy (including fluorouracil/capecitabine alone and fluorouracil/capecitabine plus oxaliplatin) in advanced-stage patients ($P < .0001$). Furthermore, after demographic match plus SES status, the percentage of 3-year survival disparity explained by tumor presentation and treatment was 36.0% and 0% for early-stage patients, whereas it was 10.4% and 45.8% for advanced-stage patients (Supplementary Table 8), respectively. These findings indicate that treatment difference mainly accounted for survival disparity in advanced-stage patients, consistent with the findings from the complete cohort (Table 3). Similar stage-specific effects also were observed when the analyses were performed after controlling for marital status and urban/rural residence, with the exception of the results of the 5-year analysis, an anomaly that most likely was owing to the small number of patients surviving for 5 years in the subcohort analyses (Supplementary Table 8). The findings of stage-stratified subcohort analyses (Supplementary Tables 7 and 8) were consistent with those derived from the complete cohort (Tables 1 and 3).

Change in Survival Disparity Over Time

We next explored the change of survival disparity over time. Because the most important chemotherapy medicine oxaliplatin and targeted agent bevacizumab both were approved by the Food and Drug Administration in 2004,[29,30] these agents have been used frequently in clinics since 2004,[31] which also is consistent with the SEER–Medicare data (Supplementary Table 9). We then used the year of diagnosis in 2004 as the cut-off point to separate the patients into 2 groups: diagnosed before 2004 (1998–2003) and diagnosed in 2004 or later (2004–2009), similar to the approach used in the study by Silber et al.[21] This approach divided all patients into approximately 2 halves (3039 black patients diagnosed before 2004 vs 3151 black patients diagnosed in 2004 or later). The change in survival disparity over time is shown in Supplementary Figure 4 and the detailed numbers are listed in Supplementary Table 10. From these new data we could see several points clearly. First, as expected, significantly better survival was observed in both black and white patients who were diagnosed in 2004 or later than in those diagnosed before 2004 (Supplementary Figure 4), which shows the effectiveness of the use of oxaliplatin plus fluorouracil/capecitabine and target therapy in colorectal cancer treatment, and is consistent with numerous published reports.[32–38] Second, the racial survival disparity was smaller in the patients diagnosed in 2004 or later than in those diagnosed before 2004, indicating that the use of oxaliplatin and/or bevacizumab helped to reduce the racial survival disparity (Supplementary Table 10) (eg, in a demographic match, the 2-, 3-, and 5-year survival disparity was 8.3%, 8.5%, and 9.6%, respectively, in the patients diagnosed before 2004, whereas it was 5.6%, 6.5%, and 7.1%, respectively, in those diagnosed in 2004 or later). This effect was consistent with a major finding of our study that the effect of treatment on survival disparity was much more apparent in advanced-stage patients because both oxaliplatin and bevacizumab

were approved and commonly used in advanced-stage but not early-stage patients. In addition, we found that tumor presentation had a much larger effect than treatment on survival disparity in the patients diagnosed both before and after 2004 (Supplementary Table 10), which was consistent with the major findings for the complete cohort.

Discussion

The causes of the known disparities in incidence and outcomes for black compared with white colon cancer patients have remained an unresolved issue for decades.[3] Many efforts have been devoted to unravel the determinants of such disparities so that appropriate policies and interventions can be designed to minimize the racial disparity, and thereby improve outcomes for black patients. As a broadly recognized driver of colon cancer racial survival disparity, socioeconomic and sociodemographic status may affect many contributing factors, such as lifestyle, concurrent/comorbid medical conditions, stage at diagnosis, tumor characteristics, health care utilization, and treatment.[17,39] Despite many years of efforts, the survival disparity between black and white CRC patients is still widening.[3] Therefore, better understanding of the role played by each possible mediator of racial survival disparity downstream of SES is necessary to help determine how interventions should be tailored to reduce this disparity.

Differences in the biological behavior of colon cancer also may contribute to survival disparity mediated by cancer stage at initial presentation. For example, colon cancer may occur at a significantly younger age in black patients compared with white patients, with black patients having approximately double the proportion of colon cancers diagnosed before the age of 50 (10.6% vs 5.5%).[40] This observation has prompted new recommendations from the American College of Gastroenterology such that the current standard of care for screening for colon cancer is actually a function of race, with white average-risk patients recommended to undergo a first screening colonoscopy at age 50 but black average-risk patients to undergo a first screening colonoscopy at age 45.[41] Although the observation that colon cancer may occur at an earlier age in black patients may be explained partly by factors related to SES, such as diet, further differences in distribution of colon cancer lesions in black vs white patients argue that there is likely a biological component as well. There is evidence that black patients may be predisposed to more proximal colon cancers in comparison with white patients who are more likely to develop more distal disease.[42] Notwithstanding these lines of evidence suggesting that there may well be a difference in the biological behavior of colon cancer in black vs white patients, the relative importance of this contributor to the well-documented disparity in survival is unclear,[43] and our current study is geared specifically to investigate those contributors driven by modifiable factors rather than genetic factors.

One important factor affected by SES is cancer stage at diagnosis. Patients with a higher SES tend to have higher health care utilization and higher CRC screening rates,[44,45] which makes them more likely to be diagnosed at an earlier stage compared with those with lower SES. Some studies have suggested that SES affects CRC survival disparity through stage at diagnosis only, with no additional influence after stage is controlled.[17,39] Our results indicate that tumor presentation, including tumor stage, is indeed one of the most important factors contributing to the racial disparity in colon cancer survival. We observed that, after controlling for demographic factors, black patients in comparison with white patients had a significantly higher proportion of stage IV and lower proportions of stages I and II disease (Supplementary Table 2). Adequately matching on tumor presentation variables (eg, stage, grade, size, and comorbidity) significantly reduced survival disparities (Table 2). These data are highly consistent with previous studies showing that tumor stage explains a significant portion, but not all, of CRC racial survival differences.[17,39,45]

Treatment disparity is another possible source of colon cancer survival disparity related to SES.[11–13] There is compelling evidence showing that treatment disparity exists between black and white CRC patients. Compared with whites, black CRC patients are less likely to receive surgical resection or radiation treatments,[46] and are treated less frequently with standard chemotherapy.[47–50] Disappointingly, the treatment gap between blacks and whites remained unaltered between 1992 and 2002, despite many mitigation efforts.[50,51] Our finding that the presentation-matched whites had higher rates of most treatments than blacks is consistent with previous studies suggesting that black CRC patients still are likely to be undertreated.[46–50] However, it should be noted that the absolute differences in the receipt of some treatments are small, which also were reported in other studies such as that by Silber et al.[21] These small absolute differences in treatment might be part of the reasons that, although treatment differences were significant in early-stage patients (Table 1), they had little effect on survival disparity. In contrast, the absolute differences of treatment disparities in advanced-stage patients were much larger. These data are in line with our conclusion that the impact of treatment differences on survival disparity was more prominent in advanced-stage patients.

Stratified analysis by cancer stage showed sharp differences of treatment disparity between early- and advanced-stage patients, in that early-stage patients usually had disparity in surgery rate whereas advanced-stage patients showed heavy disparity in the use of chemotherapy and targeted therapy (Table 1). These findings were consistent with clinical practice guidelines that predominantly use surgery in early-stage and chemotherapy in advanced-stage patients. Although, after presentation match, white patients received more of some treatments in stage I (use of surgery) and stage II (use of chemotherapy) patients, most differences were modestly significant with small PRs (Table 1). In comparison, most differences in the use of chemotherapy agents in advanced-stage patients were highly significant with high PRs. For example, the use of fluorouracil/capecitabine plus oxaliplatin in both stages III and IV was significantly different in black vs white patients (Table 1). These data derived from 1998 to 2009 were similar to the previously reported racial difference in the

use of standard chemotherapy from 1992 to 2002,[51] disappointingly suggesting that despite of the many efforts made recently, the disparity in the use of chemotherapy in advanced-stage colon cancer patients has not been improved meaningfully. These data echo another important conclusion made in our study that the percentage of survival disparity after demographic match explained by treatment is much higher in advanced-stage than early-stage patients (Table 3 and Supplementary Figure 1). Taken together, these lines of evidence suggest that, to control survival disparity, more efforts may need to be tailored to minimize treatment disparities (especially chemotherapy use) in patients with advanced-stage disease. Nevertheless, it should be borne in mind that although it is ideal to eliminate all racial treatment disparities, there will be a point of diminishing return-to-efforts ratio to ensure the appropriate delivery of cancer treatment for all patients.

Our subcohort analyses, which adjusted either SES or marital status and urban/rural residence, provided us with important clues as to the effects on racial survival disparity by different contributing factors. Highly consistent with the results of the analyses derived from the complete cohort, tumor presentation also played a much stronger role on survival disparity than treatment in the subcohort analyses. For example, in the analyses that controlled SES, the 2-, 3-, and 5-year survival rate after tumor presentation match was 35.4%, 24.2%, and 48.1%, respectively. After further treatment match, the survival disparity was -1.5%, 8.1%, and -6.5%, respectively. A very similar phenomenon was observed in the analyses that controlled marital status and rural/urban residence. Nonetheless, it should be noted that these analyses were derived from the subcohort of only 2000 black patients and needed to be confirmed in larger studies.

The underlying reasons for racial disparity are complex and difficult to decipher and need even larger prospective studies with more homogenous patient characteristics (ideally randomized controlled trials). However, currently it may not be feasible to conduct such studies, especially in prospective settings. The SEER–Medicare data set, although not perfect, is one of the largest available resources that may help decipher some of the reasons for racial survival disparities. Our findings that larger treatment differences were observed in advanced-stage patients provided one stepping stone toward a better understanding of the complex natures of racial survival disparities in colon cancer. Nevertheless, treatment differences might be, to some extent, a reflection of other racial differences, such as physician-patient communication and patient attitude. Mitigating these disparities will require continued efforts in patient education and navigation that would help both physicians and patients to work together toward informed decision making regarding their treatments.

The novel minimum distance-based matching strategy was a major strength of our study. Most racial disparity studies used model-based methods. With white patients constituting the majority of the study population, utilization of such models to explain racial disparity may be limited.[21] During the matching, we also used propensity scores to calibrate the distance before assigning whites to blacks according to minimum distance. This method is different from the propensity score matching method, which tends only to balance all of the observed covariates used to define the score in a stochastic sense similar to random assignment.[52,53] By incorporating propensity score, the minimum distance method not only balances the observed covariates in a stochastic sense, but also achieves close matches on individual key covariates.[54] Another strength of our study was the large patient cohort size in the SEER–Medicare database, which allowed us to focus the analysis on colon cancer and exclude rectal cancer, eliminating potential confounding effects from the differences between these 2 subtypes, especially regarding treatment.[55]

A major limitation was that because of the drastic differences of SES, as well as other important variables such as marital status and urban/rural residence between black and white patients, we were unable to control all of them in the primary matching analyses. Therefore, the primary findings of this study still are subject to residual confounding, which warrants further explorations. It is apparent that, even in the subcohort analyses, there is still remaining survival disparity after treatment match (3.7%, 2.4%, and 3.3%, respectively, for the 2-, 3-, and 5-year survival rates in Table 4, and 4.7%, 4.3%, and 5.2%, respectively, in Supplementary Table 6). The residual disparity could be explained by factors that were not controlled in the analyses. SEER data do not collect information on other potentially important confounders such as the use of over-the-counter medications and oral prescription drugs,[56] provider- and facility-related characteristics,[57] as well as genetic,[58] dietary,[59] environmental,[14] and biological factors.[17] A more complete assessment of major underlying factors is needed to inform the development of strategies that can further reduce or even completely eliminate the racial disparity in colon cancer survival.

In conclusion, we present evidence that in the SEER–Medicare population, black colon cancer patients received significantly less treatments than white patients, and this treatment disparity showed a dramatic impact on survival disparity in advanced-stage but not early-stage patients. For all stage-combined patients, the differences in survival appear to be related primarily to tumor presentation characteristics at diagnosis rather than treatment differences. These findings suggest that reducing the treatment disparity is important to mitigate the racial survival disparity in advanced-stage colon cancer patients. However, for the overall colon cancer population, tumor presentation may play a more prominent role. To reduce the survival disparity between black and white colon cancer patients, more effort is needed in areas such as disease biology and CRC screening to reduce the tumor presentation disparities between black and white patients.[2,3,60]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.01.030.

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Received September 23, 2014. Accepted January 24, 2016.

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Conflicts of interest
The authors disclose no conflicts.

Funding
Supported by grants from the Pennsylvania Department of Health (HRFF 09F RFA-08-07-06), Thomas Jefferson University, National Cancer Institute (CA162201), and an American Cancer Society Research Scholar grant (123741-RSG-13-003-01-CCE).